REMARKS

Reconsideration of the allowability of the present application is requested respectfully.

Status of the Claims

Claims 21 to 25, 27 to 31, 33, 35, 38, 39, 41 and 42 were acted upon by the Examiner in the Office Action dated September 11, 2003. No claims are withdrawn. Claims 38, 39, 41, and 42 have been amended. No claims have been canceled. Claim 43 has been added. Accordingly, Claims 21 to 25, 27 to 31, 33, 35, 38, 39, and 41 to 43 are presented for examination.

Support for Amendments to the Specification

Support for the text to be added to page 6 is found in originally filed claims 6 and 12.

The other amendments to the specification are editorial in nature and as such do not constitute new matter.

Support for Amendments to the Claims

The amendments to Claims 38, 39, 41, and 42 are editorial in nature and as such do not constitute new matter.

Support for New Claim

Support for new Claim 43 is found from page 4, line 23, to page 5, line 14.

ARGUMENTS

In response to the Examiner's Office Action dated September 11, 2003, Applicant respectfully traverses the Examiner's rejection of Claims 21 to 25, 27 to 31, 33, 35, 38, 39, 41, and 42.

Objection to Reference to Figure 7

The Examiner has objected to reference to "Figure 7" on pages 7 and 24. Reference to "Figure 7" has been deleted from these pages.

The §112, First Paragraph (Enablement) Rejections

The Rejection of Claims 21 to 25, 27 to 31, 33, 35, 38, 39, 41, and 42

The Examiner has rejected Claims 21 to 25, 27 to 31, 33, 35, 38, 39, 41, and 42 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make or use the invention.

Applicant respectfully traverses the rejection.

The independent claims at issue, that is, Claims 21 and 28, are directed to methods wherein at least a first and a second subpopulation of micro(nano)particles are administered to a subject. Each of the micro(nano)particles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the micro(nano)particles of the first subpopulation is different than the antigen in the micro(nano)particles of the second subpopulation.

The Examiner has asserted that the specification fails to provide any description of such a method and that no results using such a method are provided. The Examiner further asserts that the specification teaches two antigens encapsulated within the same micro(nano)particle, but not two subpopulations of micro(nano)particles each containing a different antigen. However, the Examiner does acknowledge that the specification as originally filed does disclose a method of inducing a protective immune response wherein the microparticles (or nanoparticles) comprise at least 2 subpopulations of microparticles (or nanoparticles), each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer. This disclosure is found in original claims 6 and 12. Thus, the Examiner's contention is not that the application doesn't disclose two antigens encapsulated within two separate subpopulations of the same micro/nanoparticle, but rather that the application does not disclose results from administration of two antigens encapsulated within two separate subpopulations of the same micro/nanoparticle.

In the Amendment filed February 26, 2002, Applicant has stated that support for a method comprising two subpopulations of micro(nano)particles each containing a different antigen is found in Examples 7 and 8 of the application.

On page 20, lines 23 to 24, Example 7 recites: "PTd-FHA-PLG (100 μg of each of PTd and FHA entrapped in PLGA microparticles)". The Examiner has interpreted this phrase to mean 100 μg of PTd and 100 μg of FHA encapsulated within the same microparticle. In contrast, Applicant asserts that this phrase refers to a first subpopulation of 100 μg of PTd entrapped in PLGA microparticles and a second subpopulation of 100 μg of FHA entrapped in PLGA microparticles.

Applicant respectfully submits that one of ordinary skill in the art would interpret the language of Example 7 to mean a first subpopulation of 100 μg of PTD entrapped in PLGA microparticles and a second subpopulation of 100 μg of FHA entrapped in PLGA microparticles. The Examiner is respectfully directed to originally filed Claims 6 and 12, which recite:

6. The method of Claim 1, wherein the microparticles comprise at least 2 subpopulations of microparticles, each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer.

12. The method of Claim 7, wherein the nanoparticles comprise at least 2 subpopulations of nanoparticles, each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer.

Applicant submits that these claims would put one of ordinary skill in the art on notice that portions of the application are directed to 2 subpopulations of micro(nano)particles, each subpopulation comprising a different antigen entrapped or encapsulated by a biodegradable polymer. In addition, one of ordinary skill in the art would recognize that Examples 1 to 4 all disclose preparation of micro(nano)particles loaded with only a single antigen. Example 1 (page 10, line 1, to page 11, line 29) is directed to KLH-loaded microparticles. Example 2 (page 12, line 1, to page 13, line 9) is directed to PTd-loaded microparticles. Example 3 (page 13, line 10, to page 14, line 3) is directed to FHA-loaded microparticles. Example 4 (page 14, line 4, to page 17, line 5) is directed to PTd *or* FHA loaded nanoparticles.

The Examiner is particularly directed to the antigen loading step of Example 4 on page 15, lines 18 to 20, which recites (emphasis added) "A PTd (168 μg/ml) ***or*** FHA (264 μg/ml) solution was first dispersed in a PVA (mwt = 13000-23000; 98% hydrolysis) solution while stirring at 400 rpm with the temperature set at 25°C." One of ordinary skill in the art would recognize that this alternative language indicates that the PTd and FHA solutions were used to generate two separate batches of antigen-loaded nanoparticles and not a single batch of nanoparticles loaded with both antigens. In further support of this assertion, page 15, line 18, to page 17, line 5, describes the characterizations of these two separate batches (1.2% PTd and 1.0% FHA).

Accordingly, while one of ordinary skill in the art would recognize that Examples 1 to 4 could be adapted to loading more than one antigen into a micro(nano)particle (see page 5, lines 28 to 29), one of ordinary skill in the art would know that all of the antigen-loaded micro(nano)particles generated by Examples 1 to 4 comprise only single antigens encapsulated in micro(nano)particles. Knowing this, Applicant submits that upon reading the phrase "PTd-FHA-PLG (100 μg of each of PTd and FHA entrapped in PLGA microparticles" in Example 7, one of ordinary skill in the art knows that this phrase refers to a first subpopulation of 100 μg of PTd entrapped in PLGA microparticles and a second subpopulation of 100 μg of FHA entrapped in PLGA microparticles.

In view of the above, Applicant submits that the data shown described in Example 7 and shown in Figure 6, are representative of experimental results using two subpopulations of microparticles each containing a different antigen. Accordingly, in contrast to the Examiner's assertions, this subject matter was

described in the specification in such a way as to enable one skilled in the art to make or use the invention.

Applicant has also stated that support for a method comprising two subpopulations of nanoparticles each containing a different antigen is found in Example 8 of the application.

Page 21, lines 17 to 18, of Example 8 recites: "Treatment 2:PTd + FHA in PLGA (blend of 100 μg of each of antigen entrapped in nanoparticles according to Example 4)". As noted above, the "antigen entrapped in nanoparticles according to Example 4" refers to PTd ***or*** FHA entrapped in nanoparticles. Specifically, the "antigen entrapped in nanoparticles according to Example 4" would be batches 1.2% PTd and 1.0% FHA described on page 16 in Tables 3 and 4. Accordingly, as the nanoparticles of Example 8 are the nanoparticles of Example 4, and the nanoparticles of Example 4 are each loaded with only a single antigen, then the nanoparticles of Example 8 must also only be loaded with a single antigen.

Further support of this assertion is found in Example 8 on page 24, lines 11 to 12, which recites (emphasis added): "They reveal a high level of protection in animals orally immunised with a blend of nanoparticles entrapping PTd and FHA ***respectively***." The use of the term "respectively" in this sentence indicates nanoparticles entrapping either PTd *or* FHA, not PTd *and* FHA.

In view of the above, Applicant submits that the data shown described in Example 8 is representative of experimental results using two subpopulations of nanoparticles each containing a different antigen. Accordingly, in contrast to the

Examiner's assertions, this subject matter was described in the specification in such a way as to enable one skilled in the art to make or use the invention.

The Examiner has also asserted that the specification is not enabled for methods which use *any* antigens in the immunization methods. Applicant submits that one of ordinary skill in the art would recognize that the present invention can be utilized with not just PTd or FHA as antigens, but with any antigen. Page 8, lines 14 to 23, of the application lists some representative examples of antigens. Given the teachings found in Examples 7 and 8, one of ordinary skill in the art would be able to utilize any given antigen and test that antigen for efficacy in the context of these examples. As Jones et al., Eckhardt et al., Singh et al., and Shahin et al. (cited in the present office action) and Anderson et al., Clemens et al., and Ferreccio et al. (cited in the IDS dated July 30, 2003) indicate, methods of determining whether a protective immune response has been induced by treatment of a subject with an antigen are well known in the art. The prior art in addition to the data and results shown in Examples 7 and 8 and in Figure 6 would indicate to one of ordinary skill in the art how to use the claimed invention using any antigen.

The Examiner has also invited Applicant to submit additional evidence to enable the scope of the invention. In this regard, enclosed is a copy of Figure 7, which is referred to in the originally filed application on page 7, lines 21 to 28, and page 24, line 3, and provides an illustration of some of the results generated in Example 8.

The §103(a) Rejections

The Rejection of Claims 21 to 25, and 27

The Examiner has rejected Claims 21 to 25, and 27 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. (Infect. Immun., 1996, 64(2): 489-494) in view of Eckhardt et al. (US 5,897,867) in further view of Singh et al. (Vaccine, 1998, 16(4): 346-352) and Shahin et al. (Infect. Immun., 1995, 63(4):1195-1200).

Applicant respectfully traverses the rejection.

MPEP §2143 states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

In the present case there is no reasonable expectation that a combination of Jones et al., Eckhardt et al., Singh et al., and Shahin et al. would be successful. Furthermore, the teaching to make the claimed combination as well as the expectation of success is not found in any of the cited publications as required by MPEP §2143.

Claim 21 covers a method of inducing a protective immune response, requiring oral administration of a first and a second subpopulation of microparticles,

wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 5 μm. Claims 22 to 25 and 27 all depend from Claim 21.

Jones et al. is directed to oral administration of microencapsulated *B. pertussis* fimbriae. Jones et al. teaches that administration of *B. pertussis* vaccines to the respiratory tract e.g., intranasal administration) is not effective in stimulating production of serum immunoglobulins. Furthermore, Jones et al. speculates that in regard to administration to the respiratory tract, "an unequivocal correlation between the presence of secretory antibodies and protection has not been established" (Jones et al., page 491, col. 2, para. 2, lines 13 to 14). Jones et al. also states that intranasal administration of *B. pertussis* vaccines "may not be appropriate for inducing immunity" (Jones et al., page 491, col. 2, para. 2, line 25).

In contrast to Jones et al., Shahin et al. discloses the benefits of intranasal administration of the secreted *B. pertussis* proteins FHA, pertussis toxin, and pertactin. In regard to oral administration, Shahin et al. states that administration of microencapsulated FHA fails to stimulate "a protective mucosal response via the oral route" (Shahin et al., page 1199, col. 2, para. 2, lines 12 to 13). Shahin et al. also discloses that "less than 1% of an oral dose of DL-PLG microspheres successfully reaches the Peyer's patch", indicating that oral administration of microspheres is a poor route for inducing immunity (Shahin et al., page 1199, col. 2, para. 2, lines 15 to 16). Furthermore, Shahin et al. states that "Respiratory immunization with antigens...has been a successful strategy for the induction of both

systemic and mucosal immune responses" (Shahin et al., page 1199, col. 2, para. 3, lines 1 to 3).

Accordingly, a careful reading of Jones et al. and Shahin et al. reveals that although these publications were published within ten months of each other, they directly contradict each other. Jones et al. teaches oral administration of vaccines since respiratory administration does not work, while Shahin et al. teaches respiratory (intranasal) administration of vaccines because oral administration does not work.

MPEP §2141 states (emphasis added), "The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination". In considering Jones et al. and Shahin et al. in their entireties, it is clear that these two publications are not only in direct conflict with each other, they teach away from each other and thus teach away from the claimed invention. The Examiner states that one of skill in the art would have chosen to use the oral route taught by Jones et al. as opposed to an intranasal route, because Jones et al. discloses that the oral route is better. However, the Examiner provides no basis why one of skill in the art would discount the teachings of Shahin et al., which teaches exactly the opposite, that the intranasal route is superior, particularly when using FHA as antigen. Applicant respectfully submits that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As noted above, the publications must be considered as a whole. The Examiner has presented no objective evidence that, without the present application to use a guide, one of skill in the art would, upon reviewing Jones et al. and Shahin et al., have selectively ignored those portions of Jones et al. and Shahin et al. that are in conflict with each other. Without the present application, one of ordinary skill in the art would have

no basis to follow Jones et al. and selectively ignore Shahin et al. Applicant submits that one of ordinary skill in the art would 1) not combine publications that teach away from each other; and 2) not expect to be successful if the publications were combined.

Applicant also submits that one of ordinary skill in the art, when critically reading the data in Shahin et al., would not have an expectation of success based upon the presented data. In particular, the data allegedly supporting the claim in the abstract of Shahin et al. (administration of more than one antigen is more effective administering only one antigen) is insufficient to support an expectation of success. Table 7 on page 1199 of Shahin et al. discloses the Log_{10} CFU from the lungs and trachea of mice treated intranasally with different combinations of antigens. Taking standard deviations into account, only two combinations (FHA, PT, + pertactin and FHA + pertactin) have results that are better than administration of single antigens. However, in the FHA, PT, + pertactin combination, the results for only 2 out of 7 (lungs) and 1 out of 7 (trachea) infected mice are shown. Similarly, in the FHA + pertactin mice, the results for only 2 out of 5 and 1 out of 5 for lungs and trachea, respectively, are shown. The authors provide no explanation for their selective omission of the data for the other infected mice. Applicant respectfully submits that one of ordinary skill in the art would question to why the data from the other mice was omitted and accordingly would be skeptical as to the veracity of the data and the conclusions drawn therefrom. Thus, applicant respectfully submits that one of ordinary skill in the art would not consider Shahin et al. as a valid teaching of more than one antigen being more effective than administering only one antigen and based upon this data would not have an expectation of success.

MPEP §2141 further states (emphasis added):

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

In contrast to the Shahin et al. data, Figure 6 of the present application demonstrates, using all of their mice (see Example 7 on pages 20 to 21), that after 14 days, PT +FHA gives better than 2 Log_{10} units improvement over PT alone. Thus, in comparison to the results of Shahin et al., this result demonstrates unexpected results (applicant's data, surprisingly, shows synergism), the satisfaction of a long felt need (improved vaccination), and failure of others (the data supporting the claims of Shahin et al. are very weak).

Furthermore, Applicant submits that one of ordinary skill in the art would not combine Singh et al. with Eckhardt et al. Eckhardt et al. discloses that use of multiple antigens in a vaccine is necessary to make an efficacious vaccine.

Singh et al. discloses injection of two antigens in the same microparticle. Singh et al. does not teach that having different antigens in different microparticles is beneficial. Indeed, Singh et al., on page 350, col., 2, para. 3, lines 1 to 10, (emphasis added), recites:

> More potent antibody responses were induced with a single antigen in the microparticles rather than with two antigens in the same microparticles. One possible explanation for this observation is the presence of antigenic competition between the two antigens with the same microparticles, resulting in poorer antigen presentation. It has previously been reported that the presence of more than one antigen in a multi-component vaccine may result in reduced immunogenicity for all the antigens[32-34].

The publications cited in this passage (see "32-34" superscript at end of passage), which have all been made of record during prosecution of the instant application, all teach away from using more than one antigen. Number 32, Anderson et al. (*Vaccine*, 12: 28-31 (1994)) recites: "The combination of LPF and FHA reduced the immunogenicity of LPF" (see sentence bridging pages 30 and 31). Number 33, Clemens et al. (*JAMA*, 267:673-678 (1992)) recites: "...our data clearly demonstrate biological interference by PRP-T vaccine with immune response to pertussis whole cells in DTP vaccine..." (Page 677, col. 3, 3rd paragraph, first sentence). Number 34, Ferreccio et al. (*Pediatric Infect. Dis.*, 10:764-771 (1991)) recites: "...in this study the two vaccines appear to have interacted in a manner that somehow decreased the immunogenicity of the PRP-T" (page 770, col. 2, 2nd paragraph, last sentence). Thus, a review of the entire publication, as required by MPEP §2141, indicates that Singh et al. teaches away from using more than one antigen under any circumstances. Furthermore, Singh et al, cites three other studies that come to the same conclusion. Accordingly, one of ordinary skill in the art would not combine Singh et al. with a publication that asserts that more than one antigen improves immunogenicity (e.g., Shahin et al. or Eckhardt et al.).

Accordingly, it is clear that Singh et al. teaches away from Shahin et al. and Eckhardt et al. The Examiner's assertion that "these teachings do not suggest that two different antigens encapsulated in two different microparticles would suffer from this same antigenic competition" may be technically accurate. However, this statement does not address how one of ordinary skill in the art would be motivated to combine Singh et al. with either Shahin et al. or Eckhardt et al.

Applicant respectfully submits that the present obviousness rejection is based on a hindsight reconstruction of the present invention. As noted above, the

publications must be considered as a whole. The Examiner has presented no objective evidence that, without the present application to use a guide, one of ordinary skill in the art would, upon reviewing Singh et al., Shahin et al., and Eckhardt et al., have selectively ignored those portions of Singh et al. that are in conflict with Shahin et al. and Eckhardt et al. Without the present, one of ordinary skill in the art would have no basis to follow Eckhardt et al.'s teaching of multiple-antigen vaccines and selectively ignore Singh et al.'s teaching that multiple-antigen vaccines are less immunogenic. Applicant submits that one of ordinary skill in the art would 1) not combine publications that teach away from each other; and 2) not expect to be successful if the publications were combined.

In view of the lack of a motivation to combine Jones et al. and Shahin et al.; the lack of a motivation to combine Singh et al. with Shahin et al. or Eckhardt et al.; the lack of any expectation of success should such combinations be made; and the secondary considerations of long felt need, failure of others, and unexpected results applicant respectfully requests the withdrawal of the rejection of Claims 21 to 25, and 27 under 35 U.S.C. §103(a).

The Rejection of Claims 28 to 31, 33, and 35

The Examiner has rejected Claims 28 to 31, 33, and 35 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. in view of Eckhardt et al., Singh et al., and Shahin et al., and in further view of O'Hagan et al. (US 5,603,960).

Applicant respectfully traverses the rejection.

Claim 28 covers a method of inducing a protective immune response, requiring oral administration of a first and a second subpopulation of microparticles,

wherein each of said microparticles comprises an antigen entrapped or encapsulated by a biocompatible, biodegradable polymer, and wherein the antigen in the microparticles of the first subpopulation is different than the antigen in the microparticles of the second subpopulation and at least 50% of the microparticles are less than 600 nm. Claims 29 to 31, 33, and 35 all depend from Claim 28.

The incompatibility of the teachings of Jones et al. with Shahin et al. and Singh et al. with Shahin et al. and Eckhardt et al. is discussed above. O'Hagan et al. has been applied for the teaching of a nanospheres with mean sizes of "about 500nm" and "between 200 nm and 200 μm", respectively. The teachings of O'Hagan do not provide any motivation to combine any of Jones et al., Shahin et al., Singh et al., and Eckhardt et al. Accordingly, these teachings provide no basis to overcome the deficiencies of Jones et al. and Shahin et al., and Singh et al. and Shahin et al./Eckhardt et al. Since O'Hagan et al. does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claims 28 to 31, 33, and 35 which besides Jones et al., Eckhardt et al., Singh et al, and Shahin et al., additionally relies on O'Hagan et al.

The Rejection of Claims 38 and 41

The Examiner has rejected Claims 38 and 41 under 35 U.S.C. §103(a) as being unpatentable over Jones et al. in view of Eckhardt et al., Singh et al., and Shahin et al., and in further view of Andrianov (US 5,807,757).

Applicant respectfully traverses the rejection.

Claims 38 and 41 cover the methods of Claims 21 and 23 wherein the microparticles in each subpopulation are formed by coacervation.

The incompatibility of the teachings of Jones et al. with Shahin et al. and Singh et al. with Shahin et al. and Eckhardt et al. is discussed above. Andrianov has been applied for the teaching of a method for preparing polyphosphazene microspheres by coacervation. The teachings of Andrianov do not provide any motivation to combine any of Jones et al., Shahin et al., Singh et al., and Eckhardt et al. Accordingly, these teachings provide no basis to overcome the deficiencies of Jones et al. and Shahin et al., and Singh et al. and Shahin et al./Eckhardt et al. Since Andrianov does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claims 38 and 41 which besides Jones et al., Eckhardt et al., Singh et al, and Shahin et al., additionally relies on Andrianov.

The Rejection of Claims 39 and 42

The Examiner has rejected Claims 39 and 42 under 35 U.S.C. §103(a) as being unpatentable Jones et al. in view of Eckhardt et al., Singh et al., Shahin et al., and O'Hagan et al. and in further view of Andrianov.

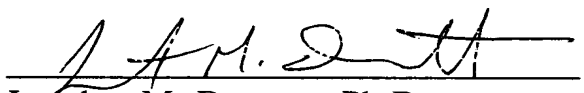
Applicant respectfully traverses the rejection.

Claim 39 covers the method of Claim 28 wherein the nanoparticles in each subpopulation are formed by coacervation.

The incompatibility of the teachings of Jones et al. with Shahin et al. and Singh et al. with Shahin et al. and Eckhardt et al. is discussed above along with the

assertion that O'Hagan et al. does nothing to overcome these deficiencies. Andrianov has been applied for the teaching of a method for preparing polyphosphazene microspheres by coacervation. The teachings of Andrianov do not provide any motivation to combine any of Jones et al., Shahin et al., Singh et al., and Eckhardt et al. Accordingly, these teachings provide no basis to overcome the deficiencies of Jones et al. and Shahin et al., and Singh et al. and Shahin et al./Eckhardt et al. Since Andrianov does not provide any information that overcomes the deficiencies in the other cited publications, applicants request respectfully withdrawal of the obviousness rejection of Claim 39 which besides Jones et al., Eckhardt et al., Singh et al, Shahin et al., and O'Hagan et al. additionally relies on Andrianov.

Respectfully submitted,



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